Tuberculosis and TNF Inhibitors

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Objectives

• Discuss the association between and epidemiology of TNF inhibitors and TB
• Discuss the challenges of diagnosing LTBI in patients on TNF inhibitors
  — TST versus IGRA
  — Risk factor assessment
• Discuss recommendations for LTBI screening of this population
• Case presentation/Discussion
Prednisone and Tuberculosis

- Risk of reactivation TB poorly defined
  - Based on anecdotal reports from 1950-70s
- CDC 2000 TB statement
  - >15mg/day for one month or more
  - Dose shown to suppress tuberculin skin test reactivity
- No observational or prospective data to support
- Retrospective studies in low incidence areas unable to demonstrate any risk of TB
Prednisone and Tuberculosis

- *Jick et al. Arthritis Rheum 2006*
- General Practice Research Database, UK
- TB cases 1990-2001 and controls†
- Current glucocorticoid use *OR 4.9 (2.9-8.3)*
  - ≤15mg/day *OR 2.8 (1.0-7.9)*
  - >15mg/day *OR 7.7 (2.8-21.4)*
  - Causal versus severity of underlying disease

*Adjusted for smoking, BMI, lung disease, diabetes, anti-rheumatic therapy, other TB risk factors
†Controls matched for age, sex, residence, time clinically followed

US Reported Infections Associated With Biologic Drugs

- Salmonellosis
- Coccidioidomycosis
- Blastomycosis
- Legionellosis
- Listeriosis
- Parasitic Infections
- Aspergillosis
- CMV
- Severe Pneumococcal Disease
- Histoplasmosis
- Invasive *Staphylococcus aureus*
- TB/NTM

CMV, cytomegalovirus; NTM, nontuberculous mycobacteria; TB, tuberculosis.
Tumor Necrosis Factor-α (TNF-α)

- Expressed by activated macrophages, T and B lymphocytes
- Biological effects numerous
  - Granuloma formation and maintenance
  - Macrophages activation to ingest and kill pathogens
- Soluble and transmembrane forms
  - Bind p55 and p75 receptors
  - p55/TNF-α interaction critical for granuloma formation

Overexpression of TNF-α

- Inflammation and tissue destruction
- Immune-mediated inflammatory diseases (IMID)
  - Rheumatoid arthritis, inflammatory bowel disease, psoriasis, ankylosing spondylitis, others
- Rewards of TNF-α blockade
  - Highly successful in treatment of these conditions
IMID Biologic Therapies

- TNF-\(\alpha\) inhibition
  - Infliximab, adalimumab, golimumab, certolizumab (monoclonal antibodies)
  - Etanercept (soluble p75 receptor)
- Newly approved
  - CD4 co-stimulation modulator: abatacept
  - B-cell (CD20+) antibody: rituximab
  - Anti-IL-6 receptor antibody: tocilizumab
  - Anti-IL12/IL23 antibody: ustekinumab

TB Risk in Anti-TNF Therapy

UK Biologic Registry

Table 2  Numbers and rates of incident tuberculosis, switchers included

<table>
<thead>
<tr>
<th>Number of patients ever received the drug</th>
<th>DMARD (n=3232)</th>
<th>All anti-TNF (n=10,712)</th>
<th>ETA (n=5521)</th>
<th>INF (n=3718)</th>
<th>ADA (n=4857)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On drug*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>7345</td>
<td>28,447</td>
<td>12,744</td>
<td>8,009</td>
<td>7,634</td>
</tr>
<tr>
<td>Cases of TB</td>
<td>0</td>
<td>27</td>
<td>5</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Rate/100,000 person years (95% CI)</td>
<td>0</td>
<td>0.06 (0.03 to 0.12)</td>
<td>0.01 (0.00 to 0.02)</td>
<td>0.13 (0.09 to 0.17)</td>
<td>0.14 (0.07 to 0.20)</td>
</tr>
<tr>
<td>IRR, adjusted for age, gender and entry year (95% CI)</td>
<td>Referent</td>
<td>3.1 (1.0 to 9.5)</td>
<td>4.2 (1.4 to 12.4)</td>
<td></td>
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</tr>
</tbody>
</table>

UK Biologic Registry


US Population-based Data

• Kaiser-Permanente Northern CA 2000-2008,
  — Anti-TNF users (n=8,418)

<table>
<thead>
<tr>
<th></th>
<th>Anti-TNF</th>
<th>ETN</th>
<th>INF</th>
<th>ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>*TB</td>
<td>49</td>
<td>17</td>
<td>83</td>
<td>61</td>
</tr>
<tr>
<td>*NTM</td>
<td>74</td>
<td>35</td>
<td>116</td>
<td>122</td>
</tr>
</tbody>
</table>

*Case rates per 100,000 pt/years; Note all 95% CIs overlap. No statistical differences between groups

KPNC background rates: TB = 2.8/100,000 and NTM = 4.1/100,000
More TB Risk with Monoclonals?

- Drug mechanisms differ
- Greater TNF-α binding
  - Transmembrane and soluble TNF-α
  - Forms stable complex
- Longer half-life
- Apoptosis of monocytes and T lymphocytes
- Interferon-gamma down-regulation
- Differential granuloma penetration

Interferon-γ Downregulation

Salu et al. JID 2006
Granuloma Penetration

A) Survival of acutely infected mice

B) Bacterial burden in the lungs

C) Survival of chronically infected mice

D) Bacterial burden in lungs

Table 1. Risk factors for prior tuberculosis exposure [15,30].

- Known prior exposure to active tuberculosis case
- Birth or extended residence in a country where tuberculosis is prevalent. This includes most countries in Latin America, Asia, the Caribbean, Eastern Europe, Africa, and Russia
- History of living or working within congregate settings where tuberculosis is more common including the following:
  - Jail or prison
  - Homeless shelters
  - Healthcare centers that treat tuberculosis patients
- History suggestive of prior LTBI diagnosis including the following:
  - Prior positive screening tests (TST, IGRA)
  - Chest radiographic findings (i.e., fibronodular opacities) associated with prior tuberculosis

LTBI: latent tuberculosis infection; IGRA: interferon-γ-release assay; TST: tuberculin skin test.
Interferon-gamma Release Assays (IGRAs)

Interferon gamma (IFN-\(\gamma\))

- Component of cell-mediated immune response
- Antigen-specific secretion
- Stable and measurable
Types of IGRA for TB

- Antigens of “RD-1” for *M. tuberculosis*
- Measure $\Delta$ IFN-$\gamma$ concentration
  - e.g. QuantiFERON®-TB Gold
    - Whole Blood stimulated with TB antigens
    - Measure IFN-$\gamma$ by ELISA
  - Measure $\Delta$ # of cells releasing IFN-$\gamma$
    - e.g. T SPOT™ (ELISpot)
    - PBMCs stimulated with TB antigens
    - Count spots

T-SPOT.TB vs. QFT-G!
### IGRA vs. TST

<table>
<thead>
<tr>
<th>IGRA</th>
<th>vs.</th>
<th>TST</th>
</tr>
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<tbody>
<tr>
<td>- <em>In vitro</em></td>
<td>- <em>In vivo</em></td>
<td></td>
</tr>
<tr>
<td>- TB specific antigens</td>
<td>- PPD</td>
<td></td>
</tr>
<tr>
<td>- No boosting</td>
<td>- Boosting</td>
<td></td>
</tr>
<tr>
<td>- 1 patient visit</td>
<td>- 2 patient visits</td>
<td></td>
</tr>
<tr>
<td>- Results in 1 day</td>
<td>- Results in 2 - 3 days</td>
<td></td>
</tr>
<tr>
<td>- Consistent readings</td>
<td>- Inter-reader variability</td>
<td></td>
</tr>
<tr>
<td>- Stimulate within 12 hrs</td>
<td>- Read in 48 - 72 hrs</td>
<td></td>
</tr>
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### IGRAs in Anti-TNF Candidates

- **Greater specificity** for tuberculosis than TST
  - Does not cross-react with BCG or most environmental mycobacteria

- **Relative sensitivity with TST for LTBI?**

  - Matulis et al, 2007¹
    - Patients with inflammatory rheumatic conditions treated with anti-TNF or non-biologic treated (n = 126)
    - 12% QFT positive vs 40% TST positive
    - QFT-IT more closely associated with LTBI risk factors than TST

¹P < .05 for comparisons. BCG, bacille Calmette-Guérin; RA, rheumatoid arthritis.

Relative Sensitivity of IGRA

- Case-control study, Peru
- 80% BCG use in both groups
- High prednisone use among RA group

<table>
<thead>
<tr>
<th></th>
<th>RA (n = 101)</th>
<th>Controls (n = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST+</td>
<td>27 (27%)a</td>
<td>61 (66%)</td>
</tr>
<tr>
<td>QFT-IT+</td>
<td>45 (45%)</td>
<td>55 (59%)</td>
</tr>
</tbody>
</table>


IGRAs in the Immunocompromised

- Anergy with TST and IGRAs
  - IGRAs less affected by prednisone?
  - False negative with IGRA in patients already receiving anti-TNF therapy1
- Indeterminate results2
  - QFT-IT and T-SPOT.TB in 2-5%
- LTBI sensitivity2
  - QFT-IT similar to T.SPOT.TB (and probably similar to or greater than TST)

Table 1. Summary of selected recommendations for tuberculosis screening prior to anti-TNF therapy

<table>
<thead>
<tr>
<th>Agency/Region</th>
<th>Year</th>
<th>Regional BCG use</th>
<th>Regional TB prevalence (cases/100,000)</th>
<th>Risk assessment</th>
<th>Initial screening test</th>
<th>Chest radiograph</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTS</td>
<td>2005</td>
<td>Yes</td>
<td>Low (12)</td>
<td>Yes</td>
<td>None</td>
<td>Yes</td>
<td>Empiric INH for those from highly prevalent regions</td>
</tr>
<tr>
<td>Switzerland</td>
<td>2008</td>
<td>Yes</td>
<td>Low (4.9)</td>
<td>Yes</td>
<td>IGRA</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>2006</td>
<td>Yes</td>
<td>Low (6.2)</td>
<td>Yes</td>
<td>IGRA</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Spanish</td>
<td>2004</td>
<td>Yes</td>
<td>Low (17)</td>
<td>Yes</td>
<td>TST (two-step)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>2009</td>
<td>Yes</td>
<td>Low (5.4)</td>
<td>Yes</td>
<td>IGRA</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>ACR</td>
<td>2008</td>
<td>No</td>
<td>Low (4.8)</td>
<td>Yes</td>
<td>TST</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>CDC</td>
<td>2005</td>
<td>No</td>
<td>Low (4.8)</td>
<td>Yes</td>
<td>TST</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>2008</td>
<td>No</td>
<td>Low (5)</td>
<td>Yes</td>
<td>TST</td>
<td>Not specified</td>
<td>IGRA in those with negative TSTs but risk factors</td>
</tr>
</tbody>
</table>

American College of Rheumatology (ACR), British Thoracic Society (BTS), National Institute for Health and Clinical Excellence (NICE), US Centers for Disease Control and Prevention (CDC).

Using both TST and IGRA maximizes sensitivity. In the presence of risk factors, any positive result is considered infected. In the absence of risk factors, all positives are considered infected except in cases of TST+/IGRA−, where history of BCG vaccination is considered. This method maximizes the predictive value of the screening tests according to a patient's prior likelihood of exposure.
TNF inhibitors and TB disease

- Anecdotally and in a few case series stated to be more likely extrapulmonary
  - Diagnosis more difficult
  - Presentation could be more severe (CNS TB)
- Patients may be more likely to have IRIS
- DR TB harder to exclude due to more cases being clinical rather than culture confirmed
- Discontinuation of TNF inhibitormay worsen underlying IMID

Case Presentation

- 70 y/o white female with long h/o RA, treated with etanercept injections q week since 2003
- TST negative prior to starting treatment (test performed by rheumatologist)
- No risk factors for TB except a few “cruises” (Caribbean and Mexico)
- Presented with left “neck” supraclavicular swelling, fevers, chills night sweats, 10 pound weight loss, slight cough and general malaise
Case Presentation

• Patient referred for excisional biopsy of the node with leading diagnosis of “lymphoma”
• Etanercept stopped
• Surgical excision of node, tissue placed in formalin and path revealed “caseating granulomas and inflammation”
• TST negative/QFT indeterminate
• CXR normal
• Exam normal except for well healing biopsy site
• Sputa x 3 for AFB sm and cx obtained

Next Steps?

• Refer for bronch
• Treat empirically for MAC
• Treat with standard four drugs for TB
• Send specimen for PCR and treat empirically for MAC
• Send specimen for PCR and treat with standard four drugs for TB
Case Presentation

• Specimen sent for PCR and patient started on standard four drug treatment for TB
• RA disabling; patient is not able to get out of bed. Wants to start Etanercept again

When to restart TNF inhibitor?

• Wait until TB treatment is complete
• Start etanercept once patient has completed the initiation phase
• Start etanercept right away
• Switch to another TNF inhibitor
Case presentation

- PCR negative
- Etanercept restarted
- Patient feels terrible; arthralgias and myalgias debilitating

What to do?

- Check LFTs
- Check Uric Acid
- Stop all TB meds
- Stop PZA
Case Presentation

- PZA stopped
- Patient immediately much improved
- Treated with HRE x 2 months and HR x 6 months (1 more month to go)
- She is much improved, has gained 10 pounds and is back to swimming and normal ADLs

Acknowledgments

- CDC — Michael Iademarco, Tom Chiller
- ACR — Dan Furst, Michael Weinblatt, Michael Weisman, Jeff Siegel
- EULAR — Josef Smolen, Paul Emery, Tore Kvien
- OHSU and KPNC — Kevin Winthrop, Cara Varley, Lisa Herrington, Roger Baxter, Liyan Liu
QuantiFERON®-TB Gold In-Tube (QFT-GIT)

Stage 1 Whole Blood Culture

- Collect 1mL of blood in 3 tubes
- Centrifuge 5 minutes to separate plasma above gel
- Collect 1mL of blood in 3 tubes
- Incubate at 37ºC for 16-24 hours.

Stage 2: Measure [IFN-\(\gamma\)] & Interpret

- Measure [IFN-\(\gamma\)] in ‘Sandwich’ ELISA
- Software calculates results and prints report

T-SPOT.TB

- Collect blood in CPT tube
- Recover, wash, & count PBMCs
- Aliquot 250,000 PBMCs to 4 wells with anti-IFN-\(\gamma\)
- Add saline, PHA, ESAT-6 or CFP-10 & incubate
- Wash away cells

Saline | ESAT-6 | CFP-10 | PHA